Are gastrointestinal stromal tumours really asymptomatic?

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Abstract

Aim: Gastrointestinal stromal tumours (GISTs) detected incidentally during abdominal surgical interventions or imaging may cause serious morbidity and mortality. We retrospectively investigated the histopathological diagnoses of GISTs made in our clinic and possible symptoms caused by the tumours prior to diagnosis. Material and Method: We retrospectively reviewed the files of patients who underwent surgery in the general surgery clinic of Kahramanmaras Sutcu Imam University between April 2012 and January 2017 and who were histopathologically diagnosed with GISTs; all were included in the study. Demographic data including age and sex, and data on preoperative complaints at the time of admission, tumour location, metastasis, local recurrence, and death were obtained. Results: The mean male and female patient ages were 57.1 ± 15.2 and 51.3 ± 15.3 years, respectively. Abdominal pain was the most common symptom (46.2%); other symptoms included weight loss, a palpable abdominal mass, constipation, incontinence, and lower gastrointestinal tract bleeding. The ileum was the most frequently involved region of the gastrointestinal tract (30.8%); other affected areas included the jejunum, lower intestinal tract, omentum, rectum, peritoneum, stomach, and pancreas. The CD117 positivity rate was 92.3%, the CD34 positivity rate was 50%, the actin positivity rate was 69.2%, and the desmin positivity rate was 15.4%. Discussion: GISTs are generally found incidentally, but they are accompanied by some symptoms in most of patients. However, as the symptoms are shared by many diseases, they are often overlooked by doctors and patients; these tumours are not diagnosed in a timely manner.

Keywords

Gastrointestinal Stromal Tumour; GIST; Symptoms; Imatinib; Prognostic Criteria; Clinical Findings

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the intestinal system [1]. GISTs are thought to originate from precursors of Cajal cells, which regulate peristalsis in the gastrointestinal tract. Mutations in the C-kit or platelet-derived growth factor receptor alpha proto-oncogenes often play roles in GIST pathogenesis [2]. However, some GISTs lack detectable mutations [3]. Such tumours frequently develop in the stomach and small intestine, less frequently in other regions of the gastrointestinal tract, and rarely outside that tract [1]. The tumours are sometimes asymptomatic until a certain size is reached and are detected incidentally during imaging performed to investigate other diseases, during elective abdominal laparoscopic procedures, or during laparotomy [4,5]. Here, we reviewed all patients diagnosed histopathologically with GISTs in our clinic to evaluate the features of such tumours and the characteristics of the patients in our region and the results of our treatments (Tables 1 and 2). We also explored the symptoms of patients with such mesenchymal tumours, which arise most commonly in the gastrointestinal system.

Material and Method

Patient characteristics

We retrospectively reviewed the files of patients who underwent surgery in the general surgery clinic of Kahramanmaras Sutcu Imam University and who were histopathologically diagnosed with GISTs. Our local ethics committee approved the study**.** All patients admitted to our general surgery service between April 2012 and January 2017 with histopathological diagnoses of GISTs were included. Patients who had been hospitalised and treated in other clinics were excluded. We reviewed the files of all included patients. Survival status was determined using the national death notification system. We reviewed outpatient data to determine whether patients had experienced relapse, and contacted patients by telephone when necessary. All data were recorded in a Microsoft Excel file.

Demographic data including patient age and sex, and data on preoperative complaints at the time of admission, tumour location at that time, metastasis status, local recurrence, and death were retrieved using our hospital information system and/or outpatient clinic records and/or via telephone conversations with patients. Death records were accessed using the hospital's electronic information system and the national death notification system (Tables 1 and 2).

To calculate the mitotic index, the numbers of mitoses in 50 magnification fields were counted; patients were sub-grouped into those with <5, 5–10, and >10 mitoses. Tumour diameters were measured by pathologists and the patients were divided into three sub-groups with tumour diameters of <5, 5–10, and >10 cm. The NIH criteria were used to assign a risk level to each subgroup. Tumours were categorised as epithelial, spindle cell, and glomus according to the relative densities of these cell types. In addition, CD117, CD34, actin, and desmin statuses (positive or negative) were evaluated, as was postoperative imatinib prescription (yes or no). Quantitative data are expressed as means ± standard deviations and medians (ranges), and qualitative data are expressed as numbers with percentages (Tables 1 and 2).

Table 1. Patients' characteristics, symptoms, imatinib treatment and life status.

No	Age	Gender	Symptom	Survey	imatinib
1	41	Male	Abd. pain	Alive	Given
2	58	Male	Abd. pain	Alive	Given
3	75	Male	Constipation	Alive	Given
4	34	Female	Abd. pain	Alive	Not given
5	74	Male	Incontinence	Alive	Not given
6	83	Male	Bleeding	Alive	Given
7	63	Female	Abd. pain	Alive	Given
8	43	Male	Weight loss	Dead	Not given
9	47	Male	Abd. pain	Alive	Given
10	52	Male	Palpable mass	Alive	Given
11	43	Male	Abd. pain	Alive	Given
12	55	Male	Weight loss	Alive	Not given
13	57	Female	Palpable mass	Alive	Nonavailable
	Mean±SD / Med (Min-Max)	Group: n(%)	Group: n(%)	Group: n(%)	Group: n(%)
	Female: 51.3±15.3/57 (34-63)	Female: 3(23.1)	Abdominal pain: 6(46.2)	Alive: 12(92.3)	Given: 8(66.7)
	Male: 57.1±15.2/ 53.5(41-83)	Male: 10 (76.9)	Weight loss: 2(15.4)	Dead: 1(7.7)	Not given: 4(33.3)
	Total: 55.8±14.7/ 55(34-83)		Palpable mass: 2(15.4)		
			Bleeding: 1(7.7)		
			İncontinence: 1(7.7)		
			Constipation: 1(7.7)		

Results

Between April 2012 and January 2017, 13 patients were histopathologically diagnosed with GISTs in our general surgery department; all were included in the present study. Ten patients were male and three were female. The mean age of male patients was 57.1 ± 15.2 [median 53.5 (range 41–83)] years. The mean age of female patients was 51.3 ± 15.3 [median 57 (range 34–63)] years. The symptoms were abdominal pain in six (46.2%) patients, weight loss in two (15.4%), palpable abdominal masses in two (15.4%), constipation in one (7.7%), incontinence in one (7.7%), and lower gastrointestinal tract bleeding in one (7.7%) patient. Four (30.8%) tumours were located in the ileum, two (15.4%) were in the jejunum, two (15.4%) were in the bowel mesenteries and omentum, two (15.4%) were in the rectum, one (7.7%) was in the peritoneum, one (7.7%) was in the stomach, and one (7.7%) was located in the pancreas (Figure 1).

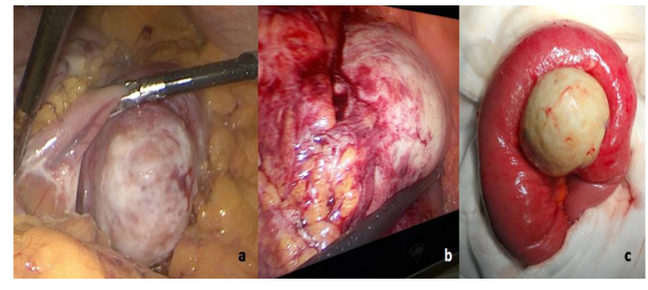

Figure 1. a) Gastric GIST b) Ileal GIST c) Jejunal GIST

Table 2. Features and classification of tumors

No	CD117	CD34	Actin	Desmin	Tumor size cm	Mitotic index	Metastasis	Classification according to risk	Localization	Pathological type
1	Negative	Positive	Negative	Negative	3	6	Liver	Middle	Omentum	Spindle
2	Positive	Negative	Negative	Negative	2.5	8	Negative	Middle	Jejunum	Epithelial
3	Positive	Negative	Negative	Negative	11.5	5	Negative	High	Rectum	Spindle
4	Positive	Positive	Negative	Negative	3	3	Negative	Low	Jejunum	Epithelial
5	Positive	Negative	Negative	Negative	2	2	Negative	Low	Rectum	Epithelial
6	Positive	Negative	Negative	Negative	6	5	Negative	Middle	Stomach	Glomus
7	Positive	Positive	Positive	Negative	6	5	Negative	Middle	Omentum	Epithelial
8	Positive	Nonavaliable	Positive	Negative	11.2	Nonavaliable	Negative	High	Pancreas	Nonavaliable
9	Positive	Negative	Negative	Positive	11	5	Negative	High	İleum	Nonavaliable
10	Positive	Positive	Negative	Positive	4.5	4	Negative	Low	Peritoneum	Nonavaliable
11	Positive	Positive	Positive	Negative	8	4	Kidney	Middle	İleum	Nonavaliable
12	Positive	Negative	Negative	Negative	4	2	Negative	Low	İleum	Nonavaliable
13	Positive	Positive	Positive	Negative	29	5	Negative	High	İleum	Epithelial
	Group: n(%)	Group: n(%)	Group: n(%)	Group: n(%)	Mean±SD / Med (Min-Max)	Mean±SD / Med (Min-Max)	Group: n(%)	Group: n(%)	Group: n(%)	Group: n(%)
	Negative: 1(7.7)	Negative: 6(50)	Negative: 9(69.2)	Negative: 11(84.6)	7.8±7.2/6 (2-29)	4.5±1.7/5 (2-8)	Negative: 11(84.6)	Low: 4(30.8)	Jejunum: 2(15.4)	Spindle cell: 2(25)
	Positive: 12(92.3)	Positive: 6(50)	Positive: 4(30.8)	Positive: 2(15.4)	Group: n(%)	Group: n(%)	Liver: 1(7.7)	Middle: 5(38.5)	İleum: 4(30.8)	Epithelial cell: 5(62.5)
					<5 :6 (46.2)	<5 : 5 (41.7)	Kidney: 1(7.7)	High: 4(30.8)	Omentum: 2(15.4)	Glomus cell: 1(12.5)
					5-10 : 3 (23.1)	5-10 : 7 (58.3)			Peritoneum:1(7.7)	
					>10 : 4 (30.8)	>10 : 0 (0.0)			Rectum: 2(15.4)	
									Pancreas: 1(7.7)	
									Stomach: 1(7.7)	

Twelve of the 13 (92.3%) patients were CD117 positive. Six of 12 (50%) evaluated patients were CD34 positive, 9 (69.2%) were actin positive, and 2 (15.4%) were desmin positive. The mean tumour diameter was 7.8 ± 7.2 (range 2–29) cm. Five of the 12 patients for whom mitotic indices were available had <5 mitoses and 7 had 5–10 mitoses. Use of the NIH criteria revealed that four patients were in a low-risk subgroup, five were in a middle-risk subgroup, and four were in a high-risk subgroup. Histopathological examination revealed glomus-type cells in one patient, spindle-shaped cells in two, and epithelial cells in five patients. Samples from the remaining five patients were not subjected to cell typing.

Seven of the 12 patients for whom data were available were prescribed imatinib as an adjuvant treatment. Twelve of the 13 patients are still alive. During follow-up, liver metastasis developed in one and kidney metastasis in another of the 12 living patients. The cause of death of the only patient who died was sudden intra-abdominal bleeding attributable to deterioration of a superior mesenteric artery (SMA) re-anastomosis on postoperative day 7. Patients' demographic data are shown in Table 1.

Discussion

Arthur Purdy Stout [6] first described GISTS, which are mesenchymal tumours thought to originate from the precursors of Cajal intestinal cells [2]. Positivity for CD117 (the C-kit marker) is very common [2,3]. In our case series, the CD117 and CD34 positivity rates were 92.3% and 50%, respectively, similar to rates described in the literature [7,8]. The actin positivity rate was 69.2%, higher than reported previously; the desmin positivity rate (15.4%) was also rather high [9-11]. However, our patient sample was small, and these proportions might not be reproduced in larger patient series.

GISTs are generally accompanied by one or more symptoms like bleeding, weight loss, abdominal pain, a sense of fullness, early satiation, and/or an abdominal mass [12]. GISTs are usually detected incidentally during imaging, endoscopy, laparoscopic surgery, and other procedures seeking to address other medical issues [4,5]. When we analysed retrospectively, all of our patients had at least one complaint at the time of referral, but these symptoms was neither specific nor diagnostic for GISTs. However, as such complaints are common, being associated with various pathologies, they are not researched adequately by patients or doctors. That is why most of our patients were diagnosed incidentally and in all cases the actual diagnosis was established after histopathologic examination.

The National Institutes of Health (NIH) classified tumours into four risk groups by reference to their diameters and mitotic indices [13,14], and the Armed Forces Institute of Pathology classified such tumours into four risk groups by reference to their diameters, mitotic indices, and locations [15]. We employed the NIH criteria for risk stratification of our patients. GISTs must be excised completely, with clear surgical margins. Any invasion

of surrounding tissue constitutes clear evidence of malignancy. Such invasions/invaginations must also be removed surgically.

All tumours with diameters ≤ 11.2 cm were removed completely and the surgical margins were clear, reflecting the ease of macroscopic visualisation, the preliminary nature of the GIST diagnosis, and our generally careful approach to surgery. One patient with a giant tumour (11.2 cm in diameter) had been referred to us because of severe weight loss. The tumour had invaded many of the major branches of the SMA; thus, we performed partial SMA resection and re-anastomosis, together with major resection of the small bowel. Thus, invasion by a GIST is an important negative prognostic factor in terms of early postoperative and long-term mortality.

Tumour cells are often delivered to the liver and lungs by the blood, growing therein to form metastases. Surgical excision remains the gold-standard treatment for GISTs [10,16,17]. Imatinib and/or the novel drug sunitinib (which promote regeneration by blocking tyrosine kinase activity), used as neoadjuvant or adjuvant treatments in patients with unresectable or metastatic tumours, increase the survival and treatment success rates [18,19]. We found no postoperative recurrence or metastasis in any patient in the low-risk group. Metastases were observed postoperatively (and not preoperatively) in two patients in the intermediate-risk group. Both patients were taking imatinib, and metastasis development suggests that they were resistant to drug treatment despite lacking mutation in the exon, as reported previously. However, we have no data on the mutational status of either patient.

Conclusion

Although GISTs are sometimes asymptomatic until a certain size is reached, they are generally accompanied by some symptoms. However, the symptoms are common to many diseases and are often ignored by patients and doctors; most tumours are diagnosed incidentally. Although the prognosis is generally good in patients in low-risk groups, moderate- to high-risk patients may develop unresectable or metastatic disease. It is important to keep in mind GISTs in differential diagnosis in patients with symptoms thought to be caused by GISTs.

Ethics Committee Approval

Ethics committee approval was received for this study from the ethics committee of Kahramanmaras Sutcu Imam University (Date: 2017/1, decision no:02).

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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